Appendix C: Research on Gulf War Illnesses: Description and Evaluation of Selected Studies

Mortality and Hospitalization Studies

[Writer, J.V., R.F. DeFraites, J.F. Brundage. 1996. Comparative mortality among US military personnel in the Persian Gulf region and worldwide during Operations Desert Shield and Desert Storm. JAMA. 275: 118-121.]

Writer et al. (1996) determined cause-specific mortality rates during the Gulf War period (August 1, 1990 through July 31, 1991) for U.S. troops deployed to the Persian Gulf (n = 688,702) and compared them with rates for U.S. troops deployed elsewhere during the same period (n = 2,590,193). Standardized mortality ratios (SMR) of age-adjusted mortality rates (deployed ÷ non-deployed x 100) and their 95% confidence intervals (95% CI) were calculated for specific causes of death. During the study period, Persian Gulf troops did not experience statistically significantly higher non-battle-related mortality rates than U.S. troops serving elsewhere, except for deaths from unintentional injury (SMR [95% CI]: 154.3 [132.0-176.7]). In the deployed troops, deaths associated with motor vehicles and aircraft accounted for about one-third and one-quarter, respectively, of deaths from unintentional injury.

[Kang, H.K. and T.A. Bullman. 1996. Mortality among U.S. veterans of the Persian Gulf war. N. Engl. J. Med. 335: 1498-1504.]

Kang and Bullman (1996) determined cause-specific mortality rates for a 2-year period after deployment [May 1, 1991 through September 30, 1993] for U.S. troops deployed to the Persian Gulf between August 1990 to April 1991 (n = 695,516) and compared them with rates for a stratified random sample of U.S. troops (active duty, National Guard, and military reserves) deployed elsewhere between September 1990 and April 1991 (n = 746,291). To compare these groups, SMRs (and 95% CIs) were calculated after adjusting mortality rates for branch of service, type of unit, age, sex, and race. A small, but statistically significant, excess of deaths from all causes was found for the deployed troops compared with the non-deployed troops (SMR = 109 [1.01-1.16]). SMRs for death from diseases (e.g., cancer, circulatory disease, or infectious or parasitic diseases) were not significantly elevated in the deployed troops, but significantly elevated SMRs were found for "all external causes" (1.17 [1.08-1.27]), "all accidents" (1.25 [1.13-1.39]), and "motor vehicle accidents" (1.31 [1.14-1.49]). Cause-specific mortality rates for either group of military personnel were consistently lower than rates for the general U.S. population, in concordance with a "healthy soldier" effect that is analogous to the healthy-worker effect observed in occupational studies. Elevated SMRs for external causes of death were found for women in the deployed (n = 49,919) group, compared with the general U.S. population, but the elevation was not statistically significant (SMR = 1.14 [0.84-1.52]).

[Gray, G.C., B.D. Coate, C.M. Anderson, H.K. Kang, S.W. Berg, F. S. Wignall, J.D. Knoke, E. Barrett-Connor. 1996. The postwar hospitalization experience of U.S. veterans of the Persian Gulf War. N. Engl. J. Med. 335: 1505-1513.]

Gray et al. (1996) compared military hospitalizations of 547,076 Gulf War-deployed and 618,335 non-deployed regular-service active-duty U.S. military personnel in 14 diagnostic categories for a period before the war and for two years after the war. Gulf War veterans were defined as those who served in the Gulf War for one or more days between August 8, 1990 and July 31, 1991. Active duty personnel were studied since they are rarely hospitalized in non DoD facilities. The comparison group of active duty, non-deployed personnel was selected randomly, except that the number of subjects selected from each service branch was proportional to the number sent to the Gulf War. The Gulf War veterans were disproportionately younger and male compared with other veterans serving in the same era; accordingly, the hospitalization and rate ratios were adjusted for age and sex. Two years before the Gulf War, those who subsequently served in that war were at slightly lower risk of hospitalization than other veterans. To control for the selection bias that resulted from deploying only the healthiest soldiers in the Gulf War, the analytical models included a covariate representing prewar hospitalization. Because of high attrition from military service after the Gulf War (due primarily to military downsizing) and the subsequent loss of follow-up, hospitalizations that occurred after September 30, 1993 were not studied. Multivariate logistic-regression models were used to analyze risk factors for hospitalization both overall and in 14 diagnostic categories (excluding diagnoses involving the reproductive system) under the International Classification of Diseases (ICD-9) system during three periods (the last five months of 1991, the entirety of 1992, and the first nine months of 1993). In each period, a subject was counted only once with regard to each diagnostic category. The overall odds ratio for hospitalization of Gulf War veterans after the war was not elevated compared with other veterans.

In an analysis that included only troops that remained on active duty for at least half of the period studied, Gulf War veterans were at greater risk than other veterans in five categories: neoplasms in 1991, diseases of the genitourinary tract in 1991, diseases of the blood and blood-forming organs in 1992, and mental disorders in 1992 and 1993 (Gray et al., 1996). The odds ratios for these categories were only slightly elevated (the maximum odds ratio was approximately 1.1 based on examination of Figure 2 in the published report) and were not consistently observed across all periods. Analysis of hospitalization rates for specific neoplasms indicated a higher standardized rate ratio (RR) for malignant neoplasms of the testis for Gulf War veterans compared with other veterans [RR = 2.12 (1.11-4.02, 95% CI)] during 1991, but not for the 1992 [RR = 1.39 (0.91-2.11)] or 1993 [RR = 0.89 (0.54-1.44)] periods. RRs for specific genitourinary system disorders were elevated during 1991, but not in 1992 or 1993. The significantly elevated RRs for specific genitourinary disorders during 1991 were: for inflammatory diseases of the ovary, fallopian tube, pelvic cellular tissue, and peritoneum [RR = 1.35 (1.11-1.63)] and for infertility [RR = 1.59 (1.19-2.11)], in female Gulf War veterans; and for redundant prepuce and phimosis [RR = 1.59 (1.22-2.07)] in male Gulf War veterans. In the 1992 period, for which an elevated odds ratio for diseases of the blood and blood-forming organs was calculated, the most

common diagnosis was for anemia. The most frequent diagnoses for the mental disorder categories were related to alcohol or other drug abuse. In summary, these analyses found elevations in risk of hospitalization for certain diagnostic categories among Gulf War veterans compared with other veterans that were not consistent across the time periods studied; thus, the findings did not clearly suggest an emerging pattern of illness in this population of Gulf War veterans.

Limitations of the Gray et al. (1996) study include:

- the study population, while large, was not a representative sample of illness in all Gulf War veterans, since it included only DoD hospitalizations of regular service, active-duty personnel (non-military hospitalizations or non-hospitalized illnesses were not included);
- the study could not detect illnesses in active-duty personnel who left the service during the period, or in Gulf War veterans who served in reserve or National Guard units;
- the study design could not detect possible associations between illnesses and geographically- or temporally-specific exposures experienced during the Gulf War;
- the study period was limited to a 2 and a half year period after the war; diseases with longer latency periods (e.g., many types of cancer) would not have been detected;
- some subjects had minimal exposure to elements of the Gulf War environment (the study population included subjects deployed to the Gulf for as little as one day); and
- the study relied on assignment of patients to ICD-9 diagnostic categories; elevated rates for a new or poorly recognized disease syndrome may not have been detected due to misclassification.

[Knoke, J.D. and G.C. Gray. 1998. Hospitalizations for unexplained illnesses among U.S. veterans of the Persian Gulf War. Emerging Infectious Diseases. 4: 211-219.]

Knoke and Gray (1998) compared post-war military hospitalization rates for diagnoses consistent with an *unexplained illness* in Gulf War deployed and non-deployed active-duty U.S. military personnel. Hospitalization records for a 4.67-year period (August 1, 1991 through March 31, 1996) were examined for 552,111 Gulf War-deployed regular-service veterans and 1,479,751 non-deployed veterans of the same era, who were on active duty for one or more days during the Gulf War period (August 8, 1990 through July 31, 1991) and retained active-duty status during the whole study period. Knoke and Gray defined an *unexplained illness* as any one of 77 ICD-9 diagnoses used by the Emerging Infections Program of the CDC to monitor death certificates for unexplained deaths; these diagnoses primarily relate to nonspecific infections (of various organ systems) and ill-defined conditions. A Cox proportional hazards model approach was used to adjust hospitalization rates for an unexplained illness for several selected covariates including categories of deployment, race, gender, military rank, and prewar hospitalization status. Deployed veterans, compared with non-deployed veterans, showed a significantly, but slight, elevated rate ratio [RR = 1.06 (1.03-1.09, 95% CI)] for hospitalization rate for an unexplained illness. When the deployed subjects who were CCEP participants were censored from the analysis, the rate ratio for hospitalization for an unexplained illness in the deployed group was no

longer elevated [RR = 0.93 (0.91-0.96)]. Knoke and Gray noted that the CCEP participants were censored, because most were hospitalized for evaluation only and not for clinical management.

Strengths of the Knoke and Gray (1998) study include the large numbers in the study population, the likelihood of few missing values since most active-duty personnel exclusively use DoD hospitals, and the relative reliability of hospital discharge as a measure of illness compared with patient report. These strengths also apply to the Gray et al. (1996) study. Limitations of the study include the first four limitations noted previously in this report for the Gray et al. (1996) study, except that the study period was lengthened to 4.67 years. Knoke and Gray (1998) also noted that some miscoding of Gulf War deployment status was evident and that the collection of diagnoses used to define unexplained illnesses was not designed specifically for the purposes of the study.

[Knoke, J.D., G.C. Gray, G.C. Garland. 1998. Testicular cancer and Persian Gulf War service. Epidemiology. 9: 648-653.]

Knoke et al. (1998) compared post-war military hospitalization rates for testicular cancer in Gulf War deployed and non-deployed active-duty U.S. military personnel. First admissions into DoD hospitals across a 4.67-year post-war period (August 1, 1991 through March 31, 1996) with a principal diagnosis of testicular cancer were reviewed among 517,223 male Gulf War-deployed regular service veterans and 1,291,323 non-deployed male veterans of the same era who were on active duty for one or more days during the Gulf War period (August 8, 1990 through July 31, 1991). All admissions with a secondary diagnosis of testicular cancer, but not a primary diagnosis, were also reviewed. There were 134 and 371 cases of testicular cancer among the deployed and non-deployed groups, respectively. A Cox proportional hazards model approach was used to adjust hospitalization rates for testicular cancer for several selected covariates including categories of deployment, race, military rank, age, and occupation. Rate ratios for hospitalization for testicular cancer in the deployed veterans compared with the non-deployed group were not significantly elevated for the total study period [RR = 1.05 (0.86-1.29)]. Probabilities of hospitalization from testicular cancer were also calculated for the deployed and non-deployed groups and examined as a function of follow-up time. This analysis showed that the deployed group had a greater risk than the non-deployed group in the early months after the war, that this increased risk persisted (but did not accelerate) for about 3 years, and that the risk was not increased by the end of the 4.67-year follow-up period. Knoke et al. (1998) speculated that the early apparent difference between deployed and non-deployed hospitalization rates for testicular cancer may have been associated with deferred medical attention during the war. Strengths and limitations of this study are similar to those previously discussed for the other Naval Health Research Center studies (Gray et al., 1996; Knoke and Gray, 1998). The limited follow-up period of 4.67 years is of particular note for a late-developing disease such as cancer. Knoke et al. (1998) noted that a survey approach will likely be required for further follow-up because of the rate of separation from active duty.

[Penman, A.D., R.S. Tarver and M.M. Currier. 1996. No evidence of increase in birth defects and health problems among children born to Persian Gulf War Veterans in Mississippi. Mil. Med. 161: 1-6.]

Anecdotal reports of increased birth defects among Gulf War veterans have been reported in the popular press; a local Jackson Mississippi newspaper reported an apparent cluster of birth defects in the infants of National Guardsmen deployed in the Persian Gulf. To document this apparent cluster, Penman et al. (1996) examined medical records of 54 of 55 children born after Gulf region deployment to 52 veterans of the two Mississippi National Guard units with the presumed birth defects cluster. The study was designed to include live births and stillbirths, but no stillbirths were reported by the veterans. The study authors concluded that the frequency of minor and major birth defects, premature births, low birth weight, and other health effects in infants appeared to be similar to reported U.S. general population rates although it does not appear that the comparisons were statistically analyzed. Interpretation of these results is confounded by the small sample size and the apparent lack of statistical analysis.

[Cowan, D.N., R.F. DeFraites, G.C. Gray, M.B. Goldenbaum and S.M. Wishik. 1997. The risk of birth defects among children of Persian Gulf War veterans. New. Engl. J. Med. 336: 1650-1656.]

Larger scale reproductive outcome studies were subsequently conducted by Cowan et al. (1997) and Aranata et al. (1997). In the Cowan et al. (1997) study, the prevalence of birth defects was examined in children of male and female Gulf War veterans (active duty in the Persian Gulf for at least one day from 8 August 1990 to 31 July 1991) and children of military personnel not deployed to the Gulf region. Medical records were examined for live births occurring in military medical treatment facilities during 1991, 1992, and 1993. Infants were included in the study if the parent(s) were active duty personnel, the births occurred before 1 October 1993, and conception occurred after the veterans returned from the Gulf region (for non-deployed personnel, the births occurred after 31 December 1990 and before 1 October 1993). No positive association between Gulf War service and the risk of birth defects were found among the 30,151 infants of male Gulf War veterans, as compared to 29,468 children of non-deployed male veterans. The risk of birth defects was slightly elevated among the 3,847 infants of female Gulf War veterans, as compared to 8,825 infants of non-deployed female veterans; the relative risk was 1.12 with 95% confidence intervals of 1.00 and 1.25. This increased risk appears to be the result of confounding by race or ethnicity, marital status, and branch of service since the relative risk was no longer statistically significant after adjustment for these variables. Additionally, the risks of severe birth defects or altered sex ratio were not significantly altered in the male or female veterans, and no relationship between risk and length of time in the Gulf region were found. Examination of only live births limits the ability of the study to conclude whether there is an association between Gulf War deployment and increased risk of birth defects because it does not record the prevalence in stillbirths or whether a pregnancy was terminated due to malformations. The Gray et al. (1996) hospitalization study used a similar study design and thus, the previously discussed limitations would also apply to the Cowan et al. (1997) study.

[Aranata, M.R.G., C.A. Moore, R.S. Olney, et al. 1997. Goldenhar syndrome among infants born in military hospitals to Gulf War veterans. Teratol. 56: 244-251.]

Using a similar design, Aranata et al. (1997) examined the prevalence of Goldenhar syndrome in 34,069 infants of Gulf War veterans and 41,345 infants of military personnel not deployed to the Gulf region. All births occurred before 1 October 1993 at military treatment facilities, the parents were still on active duty, and the infants were conceived after the veteran returned home from the Gulf region (for the non-deployed veterans, the births occurred after 31 December 1990). This study focused on Goldenhar syndrome because it was one of the congenital malformations described in the popular press reports. Goldenhar syndrome is characterized by abnormal prenatal development of facial structures; some of the features can include ear anomalies such as microtia, anotia or preauricular tags, asymmetry or hypoplasia of the face or mandible, unilateral epibulbar dermoids, colobomas of the upper lids, vertebral anomalies, and lateral facial clefts. Two pediatricians blinded to Gulf War status, examined the medical records, subsequent hospital admissions, and genetic evaluations of all infants diagnosed with an anomaly of the skull and facial bones and infants diagnosed with selected defects associated with Goldenhar syndrome. Although a higher prevalence of Goldenhar syndrome was found among the Gulf War veterans (5 versus 2 in non-deployed veterans; relative risk of 3.03 and 95% confidence interval of 0.63-20.57), the difference was not statistically significant.

Mortality and Hospitalization Studies Summary

In summary, the Naval Health Research Center's studies of hospitalization rates (Gray et al., 1996; Knoke and Gray, 1998; Knoke et al., 1998) have not found consistent evidence for increased rates of hospitalizations during a 4.67-year post-war period among Gulf War-deployed, active-duty, regular-service U.S. military personnel, compared with a referent group of non-deployed U.S. military personnel. The study populations in these studies were of sufficient size to statistically detect small differences in hospitalization rates, but, as discussed previously, several limitations shared by the studies prevent drawing any definitive conclusions regarding hospitalization rates during the same period for all U.S. Gulf War veterans.

The three available reproductive-outcome studies provide suggestive evidence that there is not a higher risk of birth defects among Gulf War veterans. However, these studies do not provide conclusive evidence due to design limitations including small sample size, inclusion of live births only, and the limited scope of the endpoints examined. Several ongoing studies (as described by Cowan et al., 1998) will hopefully address some of these limitations. These include studies examining: 1) births among separated and active duty personnel in military and civilian hospitals in seven states, 2) reproductive outcomes in a nationwide sample of veterans, 3) health of female veterans, and 4) birth defects in the children of British Gulf War veterans.

Critique of Mortality and Hospitalization Studies

[Haley, R.W. 1998a. Point: Bias from the "health-warrior effect" and unequal follow-up in three government studies of health effects of the Gulf War. Am. J. Epidemiol. 148: 315-323; Kang, H.K. and T. Bullman. 1998. Counterpoint: negligible "healthy-warrior effect" on Gulf War veterans' mortality. Am J. Epidemiol. 148: 324-325; Gray, G.C., J.D. Knoke, S.W. Berg et al. 1998. Counterpoint: Responding to suppositions and misunderstandings. Am. J. Epidemiol. 148:328-333; Cowan, D.N., G.C. Gray, R.F. DeFraites. 1998. Counterpoint: Responding to inadequate critique of birth defects paper. Am. J. Epidemiol. 148: 326-327; Haley, R.W. 1998b. Countercounterpoint: Haley replies. Am. J. Epidemiol. 148: 334-338.]

Haley (1998a) published a joint critique of the Kang and Bullman (1996) mortality rate study, the Gray et al. (1996) hospitalization rate study, and the Cowan et al. (1997) study of rates of birth defects in offspring of groups of veterans similar to those studied in the Gray et al. study. Haley (1998a) contended that the studies were biased toward finding no excess risk in deployed veterans because of: errors in calculation of confidence intervals; lack of adjustment for selection bias between deployed and nondeployed troops; and exclusion of nonmilitary hospitalizations. In reply, Kang and Bullman (1998) argued that the calculational adjustments would make no practical differences and that there was not a selection bias as noted by Haley. Gray et al. (1998) provided arguments that Haley's criticisms were based on faulty suppositions and misunderstandings of methodology and military population characteristics. Cowan et al. (1998), in reply to Haley, acknowledged that their study and other published studies of reproductive outcomes do not prove that there is no increased risk of birth defects among Gulf War veterans, but questioned the usefulness of further research in this area, in the absence of "a clearly defined hypothesis regarding measurable exposures and specific birth defects", if ongoing studies also find no positive evidence. Final responses in the debate were provided by Haley (1998b) who maintained that the three studies should be retracted and reanalyzed. Readers are referred to issue No. 4 of the *American Journal of Epidemiology* for the full commentaries.

Studies of Self-Reported Symptoms in Gulf War Deployed and Non-Deployed Veterans

[CDC (Centers for Disease Control and Prevention). 1995. Unexplained illness among Persian Gulf War veterans in an Air National Guard unit: Preliminary report -- August 1990-March 1995. MMWR. 44: 443-447.]

Late in 1994 and extending into 1995, CDC conducted an evaluation of Gulf War veterans in response to reports of unexplained illnesses among members of an Air National Guard (ANG) unit in south-central Pennsylvania (Unit A) (CDC, 1995). These veterans had reported symptoms that included rash, diarrhea, and fatigue at a local VA medical center. The purpose of CDC's evaluation was to 1) verify and characterize the signs and symptoms and 2) determine the prevalence of the signs and symptoms among members of Unit A deployed and not deployed to the Gulf, and also relative to members of other units; a third objective was to characterize the illness and identify associated risk factors; results from the third objective were presented in a

subsequent report (Fukuda et al. 1998). Comparison units were chosen for similarity in mission responsibility to Unit A and were located in Pennsylvania and Florida. Fifty-nine Gulf veterans reported to be symptomatic. Their median age was 39 years and 50 were male; all were enlisted personnel. The most frequently reported symptoms considered "moderate" or "severe" were fatigue (61%), joint pain (51%), nasal or sinus congestion (51%), diarrhea (44%), joint stiffness (44%), unrefreshing sleep (42%), excessive gas (41%),"difficulty remembering" (41%), muscle pains (41%), headaches (39%), abdominal pain (36%), general weakness (34%), and impaired concentration (34%). The symptoms reportedly began 2-3 months after departure from the Persian Gulf and persisted for $6 months. Standardized physical examination or review of medical records and accompanying laboratory tests performed at the VA medical center revealed no consistent abnormalities among the participants. Members from Unit A as well as from the three comparison units were asked to complete a questionnaire describing the frequency, duration, and severity of 35 symptoms most commonly mentioned during the first phase of the investigation and a general health history. Also, personnel who had served in the Persian Gulf were asked to provide data regarding possible exposures scenarios. A total of 3,927 personnel participated in the survey and response rates varied among units from 36% to 78%. The results of the analysis showed that in all units, the prevalence of each of 13 chronic symptoms (lasting $6 months) was significantly greater among subjects deployed to the Gulf than among those not deployed. Moreover, the prevalence of five symptom categories, chronic diarrhea, other gastrointestinal complaints, difficulty remembering or concentrating, "trouble finding words", and fatigue were significantly greater among deployed personnel from Unit A than among deployed personnel from other units. The prevalence of symptoms among non-deployed personnel was similar across units. The authors of the CDC (1995) evaluation indicated that their preliminary findings are subject to at least two limitations. First, the fact that the symptom prevalence reflected self-reported information not evaluated by physical examination and laboratory tests and, second, participation rates may have been biased towards selection of persons with symptoms leading to overestimation of prevalence of health conditions.

[Fukuda, K., R. Nisebaum, G. Stewart, W.W. Thompson, L. Robin, R.W. Washko, D.L. Noah, D.H. Barrett, B. Randall, B.L. Herwaldt, A.C. Mawle, W.C. Reeves. 1998. Chronic multisymptom illness affecting Air Force veterans of the Gulf War. JAMA. 280: 981-988.]

The results of a more complete evaluation of the cohorts examined by the CDC (1995) were recently published (Fukuda et al. 1998). This evaluation included a clinical study in which the subjects were classified as cases or noncases based on their responses to the mailed clinical epidemiological questionnaire. A major objective was to develop a case definition that captured the chronic multi symptomatic nature of illnesses in Gulf War veterans. The cross-sectional clinical evaluation included 158 Gulf War veterans (from 667 in the index unit who completed the questionnaire), irrespective of health status. The clinical case definition was identified as fatigue, difficulty remembering or concentrating, moodiness, difficulty sleeping, joint pain, and joint stiffness. A case was defined as having one or more chronic symptoms from at least 2 of 3 categories (fatigue, mood-cognition, and musculoskeletal). The clinical evaluation included psychiatric screening, physical examination, clinical laboratory tests, and serologic assays for

antibodies against viruses, rickettsia, parasites, and bacteria. The results showed a substantially higher prevalence of symptoms among Gulf War veterans than non-deployed veterans. The prevalence of mild-to-moderate and severe cases was 39% and 6%, respectively, among 1,115 Gulf War veterans compared with 14% and 0.7%, respectively, among 2,520 non-deployed personnel. Illness was not associated with time or place of deployment or with duties during the war. Fifty-nine clinically-evaluated veterans (37%) were noncases, 86 (54%) mild-to-moderate cases, and 13 (8%) severe cases. Although no physical examination, laboratory, or serologic findings identified cases, veterans who met the case definition had significantly diminished functioning and well being. A major limitation of this study, as stated by the authors, is the fact that it involved currently active duty air force personnel and cannot be generalized to other branches of service or to Gulf War veterans who have left the service. In addition, the symptoms were self-reported and may have been subject to reporting or recall bias. The finding that 15% of non-deployed also meet the case definition suggests that the multi symptom illness observed in this population is not unique to Gulf War service.

[Iowa Persian Gulf Study Group. 1997. Self-reported illness and health status among Gulf War veterans: A population-based study. JAMA. 277: 238-245.]

The Iowa Persian Gulf Study Group (1997) assessed the prevalence of self-reported symptoms and illnesses among Iowa Gulf-deployed veterans and compared these rates with those among Iowa non-Gulf-deployed military personnel. The study population consisted of 28,968 persons from which 4,886 were randomly selected from one of four study domains: Gulf-deployed regular military, Gulf-deployed National Guard/Reserve, non-Gulf-deployed regular military, and non-Gulf-deployed National Guard/Reserve. Of these 4,886 subjects, 3,695 completed a telephone interview, which was used as the means for assessing relevant medical and psychiatric conditions. Within each study domain, the population was further stratified by age, sex, race, rank, and branch of service. This resulted in 64 potential strata within each of the four study domains. The specific medical and psychiatric conditions investigated in the study were defined clearly prior to the development of the survey instrument and were based on answers to multiple questions and using accepted criteria from standardized instrument and the medical literature. Telephone interviews were conducted approximately five years after the Gulf-deployed. The relationship between each major medical and psychiatric condition and each category of exposure type were assessed using the Cochran-Mantel-Haenzel $?^2$ test. Compared to non-deployed military personnel, Gulf-deployed military personnel reported a significantly higher prevalence of symptoms of depression (17% vs 10.9%), posttraumatic stress disorder (1.9% vs 0.8%), chronic fatigue (1.3% vs 0.3%), cognitive dysfunction (18.7% vs 7.6%), bronchitis (3.7% vs 2.7%), asthma (7.2% vs 4.1%), fibromyalgia (19.2% vs 9.6%), alcohol abuse (17.4% vs 12.6%), anxiety (4.0% vs 1.8%), and sexual discomfort (1.5% vs 1.1%). In addition, assessment of health-related quality of life showed lower mental and physical scores for Gulf-deployed personnel than for non-deployed personnel. Possible explanations for the findings discussed by the authors included a distinct cause of exposure being responsible for each of the self-reported medical and psychiatric conditions; one specific psychiatric condition, such as depression, representing the primary medical condition associated with the Gulf War; exposures or prophylactic measures may have

acted synergistically with other exposures encountered in military settings causing more severe disease; Gulf War military personnel developed a multisystemic condition that does not fit well into an established category of disease; and the reported medical and psychiatric conditions among Gulf War veterans may have not been unique to the Gulf War. A final possibility discussed by the authors was that of differential recall between deployed and non-deployed personnel. Limitations of the study discussed by the authors included the fact that the study population comprised only subjects with a home record of Iowa, differential participation by selected demographic subgroups, lack of internal validation of the responses in the telephone interview, limited analysis done to compare rates of self-reported medical and psychiatric conditions among the subjects in different study domains, lack of statistical control for the number of comparisons required in the study, and no objective physical or laboratory validation of the self-reported symptoms.

[Stretch, R.H., P.D. Bliese, D.H. Marlowe, K.M. Wright, K.H. Knudson, C.H. Hoover. 1995. Physical health symptomatology of Gulf War-era service personnel from the states of Pennsylvania and Hawaii. Military Medicine. 160: 131-136; Stretch, R.H., P.D. Bliese, D.H. Marlowe, K.M. Wright, K.H. Knudson, C.H. Hoover. 1996a. Post-traumatic stress disorder symptoms among Gulf War veterans. Military Medicine. 161: 407-410; Stretch, R.H., P.D. Bliese, D.H. Marlowe, K.M. Wright, K.H. Knudson, C.H. Hoover. 1995. Psychological health of Gulf War-era military personnel. Military Medicine. 161: 257-261.]

Stretch et al. (1995) studied the effects of the Gulf War on active duty, National Guard, and reserve units in Hawaii and Pennsylvania. The evaluation was conducted by means of a questionnaire that provided self-report information on demographics, physical health symptomatology, and general psychological health. Approximately 16,167 survey questionnaires were distributed with a gross return of 31%. The subjects responded anonymously. The cohort consisted of 715 active duty and 766 reserve veterans who deployed, and 1,576 active duty and 948 veterans who did not deploy. A comparison of the percentages of both active duty deployers and non-deployers who indicated that they had experienced any of 23 physical health symptoms within the past months showed that deployed veterans reported significantly more physical health symptoms than non-deployed veterans. Similar results were found among reserve veterans. Controlling for smoking and drinking did not significantly alter the outcome of the comparisons. The differences between deployed and non-deployed veterans persisted after controlling for demographic variables such as age, rank, education, marital status, and branch of military service. The major conclusion regarding physical health was that for those who deployed to the Gulf War and currently reported physical symptoms, neither stress nor exposure to combat or its aftermath bear much relationship to their physical distress; only the fact of deployment differentiated them from those with less self-reported symptoms. Subsequent studies of this cohort by the same group of investigators showed that while deployers and non-deployers had modest differences in psychological outcomes (deployers exhibit more stress), deployment to the Gulf War did not result in any significant increases in psychological distress relative to other military personnel who did not deploy to the Gulf (Stretch et al. 1996b). The authors also reported that deployed active duty and reserve personnel had an increased likelihood of developing posttraumatic stress

disorder symptoms than non-deployed veterans (Stretch et al. 1996a). These two more recent studies also made use of the survey questionnaire methodology. The relative low participation rate in these studies obscures the significance of the results.

[Wolfe, J., S.P. Proctor, J.D. Davis, M.S. Borgos, M.J. Friedman. 1998. Health symptoms reported by Persian Gulf War veterans two years after return. Amer. J. Ind. Med. 33: 104-113.]

A recent study by Wolfe et al. (1998) investigated the possible association between opportunities for exposure and increased rates of health symptoms reporting among Gulf War veterans. The cohort consisted of subjects from the Ft. Devens ODS Reunion Survey, a longitudinal study of U.S. Army Active, Reserve and National Guard soldiers who deployed to the Gulf during 1990-1991. The study was conducted 18-24 months post-return. Of 2,313 subjects surveyed, 2,119 completed a questionnaire; nonrespondents were more likely to be on active duty status and African-American. Specifically, the authors examined the association between proxies for three wartime experiences (reported exposure to poison gas or germ warfare, being in a transportation unit, or high levels of combat exposure) and health symptoms reports after adjusting for background characteristics (i.e., gender, psychological distress). For the overall cohort, the five most commonly endorsed health symptoms on the health symptom checklist were in decreasing prevalence; aches/pains, lack of energy, headaches, insomnia, and feeling nervous and tense. In a final multivariate regression analysis, reported exposure to poison gas significantly predicted increased reports of health symptoms. Veterans who belonged to a transportation unit also were at increased risk, but the odds ratio was not significantly greater than 1. Those with higher combat exposure were not more likely to report increased health symptoms. In all models, PTSD symptomatology was significantly associated with high health symptom endorsement. However, when those with presumptive PTSD were excluded from the analysis, those who reported exposure to poison gas remained at higher risk for reporting a high number of health symptoms. The health findings in this study are consistent with those of other studies, and so are the limitations. Among the latter, the authors mention the fact that the study relied on cross-sectional data, no pre-deployment health data, exposure recall may have been affected by the time elapsed between exposure and data collection and by recall bias.

[Pierce, P.N. 1997. Physical and emotional health of Gulf War veteran women. Aviation, Space Environ Med. 68: 317-321.]

In a general health study by Pierce (1997), 484 female Air Force (active duty, reserve, or guard) veterans were asked to complete self-administered health questionnaires; the initial questionnaire was completed approximately 2 years after the war and the follow-up questionnaire was completed 2 years later (4 years after the war). The cohort consisted of 153 of the veterans deployed to the Persian Gulf region (74 and 79 were deployed in the region for less than 120 days and greater than 120 days, respectively) and 331 veterans deployed elsewhere. The general health questionnaire consisted of a list of specific symptoms which the respondent indicated the frequency of the symptoms during the last 12 months. Two years after the war, there was a statistically significant increase in the frequency of insomnia among the veterans deployed for less

than 120 days, as compared to the non-deployed veterans. The frequency of self-reported depression was also higher in this group, although no difference was found in the results of standardized measures of depression. In the veterans deployed in the Gulf region for more than 120 days, there were increased frequencies of skin rashes and unintentional weight loss. In the follow-up survey, there was a higher frequency of skin rashes among the veterans deployed for less than 120 days, but the frequency was no longer elevated in the veterans deployed for more than 120 days. Additional findings in the follow-up survey were an increased frequency of cough in both groups of deployed veterans, self-reported memory problems in veterans deployed for less than 120 days, and headaches, lumps or cysts in the breast, and abnormal Pap smear in the combined group of deployed veterans. An increased incidence of post-traumatic stress disorder (assessed using the Mississippi scale for combat-related post-traumatic stress disorder) was observed in both groups of deployed veterans 2 years after the war.

[Canadian Department of National Defence. 1998. Health Study of Canadian Forces Personnel Involved in the 1991 Conflict in the Persian Gulf. Volumes I and II. Prepared for the Gulf War Illness Advisory Committee, Department of National Defence, by Goss Gilroy Inc. Management Consultants, Ottawa. April 20, 1998. http://www.DND.ca/menu/press/reports/health/health_study_e_vol1_TOC.htm.]

A health survey questionnaire was mailed to 9947 Canadian Forces personnel, including all Canadian Gulf War veterans and a sample of Canadian Forces who served elsewhere during the Gulf War. Completed questionnaires were returned by 3113 deployed (73%) and 3439 non-deployed (60.3%) veterans. Responses between the two groups were statistically compared using logistic regression analysis to adjust for potential confounders such as age, gender and military rank. Deployed and non-deployed groups were reported to have similar socio-demographic characteristics. Gulf-deployed veterans, compared with non-deployed veterans, reported higher prevalences of symptoms of chronic fatigue, cognitive dysfunction, multiple chemical sensitivity, major depression, post-traumatic stress disorder, anxiety, fibromyalgia and respiratory diseases (bronchitis and asthma together), as well as higher numbers of children with birth defects (before, during, and after the Gulf War).

Neurophysiological and Neuropsychological Evaluations of Symptomatic Gulf War Veterans

[Axelrod, B.N. and I.B. Milner. 1997. Neuropsychological findings in a sample of Operation Desert Storm veterans. J. Neuropsychiatry. 9: 23-28.]

Axelrod and Milner (1997) examined neuropsychological performance, performance on the Minnesota Multiphasic Personality Inventory (MMPI), and subjective complaints of cognitive deficiency in a self-selected group of 44 male Gulf War veterans who were members of a National Guard reserve unit that contained 78 male veterans. Neuropsychological performance was evaluated using several measures in the general areas of intellectual functioning, achievement and language, learning and memory, and executive and motor functioning. For the group of veterans, means and standard deviations for neuropsychological measures and MMPI test scores were not

compared with measures in a matched control group but rather to clinically-accepted normal values. The study authors did not discuss the validity of the normal values or the characteristics of the populations from which they were derived. In the veterans, deficits in neuropsychological measures ($p<0.005$), relative to normal values, were observed only in finger dexterity in two of six measures of motor functioning (grooved pegboard - dominant and non-dominant) and in the Stroop color and word test, which represents three of the twelve measures of executive functioning. On the MMPI test, the only scale that exceeded a "cutoff" value of 70 in the veterans was body complaints, which is associated with reports of fatigue, concern about physical health, and specific complaints such as shortness of breath, dizzy spells, and diarrhea. Veterans with lower finger dexterity (grooved pegboard) scores (n = 15), when compared with the remainder of the group (n = 29), had lower neuropsychological performance in measures of intellectual functioning (3 of 4 measures), achievement and language (1 of 5), executive functioning (5 of 12), and motor functioning (3 of 6, including the finger dexterity deficit) and had higher scores on several clinical and supplemental scales of the MMPI, but did not differ with regard to self-reported medical symptoms or cognitive difficulties. Veterans with impaired color-word performance (n = 12), when compared with the remainder of the group (n = 32), had lower neuropsychological performance in measures of intellectual functioning (3 of 4 measures), achievement and language (2 of 5), learning and memory (2 of 9), executive functioning (10 of 12, including the color-word performance deficit), and motor functioning (4 of 6), had higher scores on several clinical and supplemental scales of the MMPI. The group with impaired color-word performance also reported a significantly higher report of recurring diarrhea but did not differ with regard to self-reported cognitive difficulties. Veterans with self-reported complaints of cognitive difficulties (n = 17), when compared with those who denied any subjective neuropsychological changes (n = 27), had lower neuropsychological performance only in measures of executive functioning but had higher scores on several clinical and supplemental scales of the MMPI (depression, organic symptoms, family problems, autism, religious fundamentalism, manifest hostility, psychoticism, suspicion, depression, resentment, tension). In summary, this group of 44 Gulf War veterans showed only minor deficits in neuropsychological performance compared with clinically-accepted normal values but had elevated psychological distress as indicated by higher scores on the MMPI. However, the findings in this study cannot definitively be extended to other Gulf War veterans or linked to service in the Gulf War because the study group was small and self-selected, no pre-deployment studies were performed on these veterans, and similar studies were not performed in a matched control group of veterans of the same era who were not deployed in the Gulf War.

[Amato, A.A., A. McVey, C. Cha, E.C. Matthews, C.E. Jackson, R. Kleingunther, L. Worley, E. Cornman, K. Kangan-Hallet. 1997. Evaluation of neuromuscular symptoms in veterans of the Persian Gulf war. Neurology. 4-12.]

Amato et al. (1997) performed neuromuscular studies in 20 Gulf War veterans who complained of severe muscle fatigue, weakness, or myalgias of 6 months duration or longer that interfered with their activities of daily living. Symptoms began 1 month to 3.5 years after returning home from the Gulf War and were present for 6 months to 3.5 years at the time of their neuromuscular

evaluation. The group of fifteen men and five women, ages 24 to 50 years, had been referred for comprehensive evaluation by specialists in neuromuscular disease from a group of 263 patients that had been evaluated by specialists in neurology, psychiatry, neuropsychology, infectious disease, and general internal medicine. The neuromuscular studies, performed by staff from the Departments of Neurology and Internal Medicine at the Wilford Hall Medical Center, San Antonio, Texas and the Departments of Medicine/Neurology and Pathology/Neuropathology at the University of Texas Health Science Center at San Antonio, included serum creatine kinase, erythrocyte sedimentation rate, thyroid function tests, graded manual muscle strength of 36 muscle groups, exercise forearm tests, nerve conduction studies, a repetitive nerve stimulation study, quantitative and single-fiber electromyography (EMG), and histologic evaluation of muscle biopsy tissues by 11 routine histologic and enzymatic stains. General physical and neurologic examinations were unremarkable, with no evidence of polyneuropathy. Six patients, five of whom were muscular males, had mildly elevated serum creatine kinase levels. Nerve conduction study results were normal except in two patients with carpal tunnel syndrome. EMG findings were normal except for one patient who had mildly-increased jitter on single-fiber EMG and also had elevated serum creatine kinase and tubular aggregates on muscle biopsy. Five patients had non-specific histologic abnormalities noted at muscle biopsy, but these histologic findings were not sufficient to diagnose an inflammatory myopathy. Electroencephalograms were normal in all patients and head CT scans and neuropsychiatric tests, performed on patients complaining of headaches, memory loss, or difficulty with concentration were also normal. Ten of the twenty patients had signs of depression or an anxiety disorder upon evaluation by psychiatry consultants. Three patients were diagnosed with somatoform disorders. One patient had atasia-abasia and documented pseudoseizures. Rheumatologists did not diagnose autoimmune or connective tissue disorders, and infectious disease consultants found no diseases. In summary, extensive neuromuscular and related studies showed no clear evidence of neuromuscular pathology in the majority of 20 Gulf War Veterans who had been referred for comprehensive evaluation by specialists in neuromuscular disease because of subjective complaints of severe weakness or myalgias that limited activities of daily living. This study is limited by the small size of the study group and the apparent absence of blinded evaluation.

[Haley, R.W., T.L. Kurt, J. Horn. 1997a. Is there a Gulf War Syndrome? Searching for syndromes by factor analysis of symptoms. JAMA. 277: 215-222; Haley, R.W., J. Horn, P.S. Roland, W.W. Bryan, et al. 1997b. Evaluation of neurologic function in Gulf War veterans. A blinded case-control study. JAMA. 277: 223-230; Haley, R.W. and T.L. Kurt. 1997. Self-reported exposure to neurotoxic chemical combinations in the Gulf War. JAMA. 277: 231-237.]

In a series of three studies, a group of 249 U.S. Gulf War veterans answered questions about health symptoms and wartime exposures and questions from a standardized psychological personality assessment questionnaire (Haley et al., 1997a,b; Haley and Kurt, 1997). The 249 respondents were part of 606 Gulf War veterans of the 24th Reserve Naval Mobile Construction Battalion living in five southeast states. Serious health problems were reported by 175 of the respondents.

In the first study (Haley et al., 1997a), principal factor analysis of the reported symptoms identified six possible syndromes of suspected neurologic injury and identified the syndromes in 63 subjects. The three syndromes with the strongest associations (the other three syndromes were reported to display only weak associations among symptoms) were given the following names: *impaired cognition* (associated with: attention, memory, and reasoning problems; insomnia; depression; daytime sleepiness; and headaches), *confusion-ataxia* (associated with thinking problems; disorientation; balance disturbances; vertigo; and impotence), and *anthro-myo-neuropathy* (associated with: joint and muscle pain; muscle fatigue; difficulty lifting; and extremity paresthesias).

In the second study, Haley (1997b) used the syndrome definitions to compare results in batteries of neuropsychological, neurological, clinical, and blood tests between cases and controls. "Cases" were defined as the subjects with the five highest symptom scores among those with *impaired cognition* and those with *arthro-myo-neuropathy* (i.e., 5 cases from each group), and the subjects with the 13 highest symptom scores among those diagnosed with *confusion-ataxia*. The 20 controls were matched for age, sex, and educational level to cases in the *confusion-ataxia* syndrome, and the administrators of the tests were blinded as to group identity of the subjects. Haley et al. (1997b) noted that the *confusion-ataxia* syndrome was oversampled because this syndrome appeared to be more disabling than the other two syndromes. Motor and reflex functions were evaluated clinically. Neurological examinations included: tests of auditory and vestibular function, brain stem auditory evoked potentials, somatosensory and visual evoked potentials, and brain imaging (magnetic resonance imaging and single-photon emission computed tomography). The Halstead-Reitan test battery evaluated neuropsychological endpoints. Blood tests included complete hematology and numerous biochemical variables including activities of creatinine kinase, butyryl cholinesterase and red blood cell cholinesterase, and acetylcholine receptor antibody level.

The frequency of abnormalities in the various blood tests or in the brain images were not significantly different between cases and controls (Haley et al., 1997b). Clinical neurological examinations found no statistically significant differences between the cases and controls, except that 6/22 cases showed weakness of the lower extremities (one case was excluded from the analysis because of conscious efforts "to embellish the examination"), compared with 1/20 in the control group. Based on neuropsychological test results, mean scores on the Halstead Impairment Index and the General Neuropsychological Deficit Scale were statistically significantly greater in cases than in controls, indicating greater neuropsychological dysfunction. In auditory and vestibular function tests, the frequency of cases with abnormal ocular motility was not significantly different from controls, but significantly more controls (4/23) showed abnormal spontaneous nystagmus (rhythmic movement of eyeball) than cases (0/20). Cases, statistically compared with controls, showed significantly diminished velocity of nystagmus in response to stimulation of the ear by heat or cold and significantly increased interocular asymmetry of saccadic velocity and of nystagmus in response to rotation. The frequencies of subjects with abnormal values of somatosensory-evoked-potential variables or brain stem auditory-evoked-potential variables were not significantly different between cases and controls, but statistically

significant differences were found between cases and controls for mean values for several of the variables (e.g., greater interside asymmetry of the wave I to wave II interpeak latency of brain stem auditory evoked potentials, and increased latency of the lumbar-to-cerebral peaks on posterior tibial somatosensory evoked potentials). The clinical significance of the differences observed between cases and controls is uncertain. Six neurologists, who were blinded to the identity of the subjects, reviewed the findings on each individual and concluded that "the clinical and laboratory findings were nonspecific and not sufficient to diagnose any known syndrome in any subgroup of the subjects." Nevertheless, Haley et al. (1997b) speculated that the observed statistically significant differences between cases and controls in several objective measures of neurophysiological and audiovestibular variables may have a relationship with "sublethal exposures to cholinesterase-inhibiting chemicals", and noted that additional research is necessary, including examining the same, and additional, endpoints (e.g., neuromuscular and nerve conduction velocity variables) in a greater number of subjects (cases and controls).

In the third study, Haley and Kurt (1997) used self-reported exposure information (e.g., exposure to pesticides, chemical weapons, smoke from oil well fires, and pyridostigmine bromide) from the 249 Gulf War veterans to look for statistical associations between exposure to risk factors and the occurrence of the three "factor analysis-derived syndromes" described earlier. Statistically significantly increased relative risks (RR) were reported for the:

- *impaired cognition* syndrome in those who reported wearing pet flea-and-tick collars [RR = 8.2 (95% CI = 2.9-23.5)] and those whose main job involved security [RR = 6.4 (2.1-19.30)];
- *confusion-ataxia* syndrome in those reporting experiencing a likely chemical weapons attack [RR = 7.8 (2.3-25.9)], those located in sector 7 in northeastern Saudi Arabia on January 20, 1991 [RR = 4.3 (1.9-10)], and those reporting severe advanced adverse effects from pyridostigmine bromide [RR = 32.4 (7.8-135)];
- *arthro-myo-neuropathy* syndrome in those reporting typically applying a relatively large amount of insect repellent to the skin [RR = 7.8 (2.4-24.7)] and those reporting severe advanced effects from pyridostigmine bromide [RR = 3.9 (1.3-12.1)].

Haley and Kurt (1997) concluded that the findings provide support for the hypothesis that the three factor analysis-derived syndromes may represent variants of organophosphate-induced delayed neuropathy due to exposure to mixtures of anti-cholinesterase agents (pesticides, insect repellent, and pyridostigmine), acknowledging the limitation of the self-reported nature of the exposure determinations.

Mycoplasma and Bacterial Infections in Gulf War Veterans with Illnesses: Detection and Treatment

[Nicolson G.L., N.L. Rosenberg-Nicolson. 1995. Doxycycline treatment and desert storm. J. Amer. Med. Assoc. 273:618-619.]

Prior to conducting studies on detection of mycoplasma in Gulf War veterans, Nicolson and Rosenberg-Nicolson (1995) suggested that many of the health complaints of Gulf War veterans listed by the report of the NIH Technology Assessment Workshop Panel (1994a,b) might be associated with aggressive pathogenic mycoplasma infections such as *Mycoplasma incognitus* or *Mycoplasma penetrans*, and that such infections should be treatable with multiple courses of antibiotics such as doxycycline or macrolides. Nicolson and Rosenberg-Nicolson (1995) also reported that they conducted a phone/letter survey of 73 Gulf War veterans who had the symptoms listed by the NIH Technology Assessment Workshop Panel (1994) and that 55 of the 73 indicated that "they had good responses with doxycycline and eventually returned to normal duty." No firm conclusions can be drawn from this uncontrolled survey study because no additional information was reported to characterize these patients, the antibiotic treatment regimen they received or what constituted a good response. In addition, the subjective reports of good responses cannot clearly be linked to suppression of mycoplasma infection, since doxycycline would be expected to be effective against other unrecognized organisms.

[Nicolson, G.L. and N.L. Nicolson. 1996. Diagnosis and treatment of mycoplasmal infections in Persian Gulf War illnesses - CFIDS patients. Intl. J. Occup. Med. Immunol. Toxicol. 5: 69-78.]

Nicolson and Nicolson (1996) used a Gene Tracking technique to assess the presence of mycoplasma gene sequences in the nuclei of leukocytes isolated from blood samples from 30 Gulf War veterans with symptoms of Gulf War illness or symptomatic members of their families (collectively referred to as Gulf War illness patients) and from 21 "normal controls". No objective data were provided to characterize the medical histories or general medical condition of the test subjects at the time of the study. Mycoplasma gene sequences were detected in 14/30 Gulf War illness patients but were not detected in the normal controls. Using probes for *Mycoplasma fermenting* (incognitus strain), *M. genatalium, A. laidwaii*, and other mycoplasmas, 9/14 mycoplasma-positive patients were found to have gene sequences only for *Mycoplasma fermenting* (incognitus strain). Treatment suggestions for each of the 14 mycoplasma-positive patients were made to primary care physicians. Eleven of the 14 mycoplasma-positive patients were reported to have completely recovered after multiple cycles of treatment with doxycycline or ciprofloxacin antibiotics. Case reports of the symptoms, course of treatment, and outcome were presented for 11/14 treated patients. Upon retesting of four of the patients who were reported to have completely recovered after antibiotic therapy, no evidence of mycoplasma gene sequences was found in their blood leukocytes.

[Nicolson, G.L., N.L. Nicolson, M. Nasralla. 1998. Mycoplasmal infections and fibromyalgia/chronic fatigue illness (Gulf War Illness) associated with deployment to Operations Desert Storm. Int. J. Med. 1:80-92; Baseman, J.B. and J.G. Tully. 1997. Mycoplasmas: Sophisticated, reemerging, and burdened by their notoriety. Emerging Infect. Dis. 3: 21-32.]

In a study similar to that of Nicolson and Nicolson (1996), Nicolson et al. (1998), using the Gene Tracking method to assess the presence of mycoplasma gene sequences in the nuclei of leukocytes isolated from blood samples, found evidence of mycoplasma gene sequences in 76/170 Gulf War

veterans and symptomatic members of their families who had signs and symptoms of Gulf War illness/fibromyalgia/chronic fatigue syndrome and in 2/41 members of a control group of "nondeployed, healthy adults". It was not indicated whether or not the control group consisted of veterans of the Gulf War era who had not been deployed in the Gulf War. It was also not clear if the results for the group of 170 included results from a group of 30 Gulf War veterans and symptomatic family members that were reported previously by Nicolson and Nicolson (1996). Nicolson et al. (1998) also reported the presence of mycoplasma gene sequences in 2/2 British veterans with symptoms of Gulf War illness/ chronic fatigue syndrome but did not comment further on these subjects. Gene sequences characteristic of *Mycoplasma fermenting* were reported to have occurred in "about 2/3" of the Gulf War illness patients. Treatment of 73 of the mycoplasma-positive patients with multiple cycles of doxycycline, ciprofloxacin, or azithromycin was reported to result in recovery in 58 patients after two to six treatment cycles. Criteria for recovery were not presented. Case reports of the symptoms, course of treatment, and outcome were presented for seven of the patients who received antibiotics. Upon retesting of 19 of the patients who were reported to have recovered after antibiotic therapy, no evidence of mycoplasma gene sequences was found in their blood leukocytes.

General limitations of the studies by Nicolson and colleagues include:

- Blind testing of specimens from Gulf War veterans was not performed and appropriate control groups were not studied to determine whether or not infection with mycoplasma is associated with either illness or participation in the Gulf War. The inclusion of healthy referent groups seems important since mycoplasma species appear to comprise normal microbial flora of healthy persons (Baseman and Tully, 1997).
- The sensitivity and reproducibility of the Gene Tracking method for detection of mycoplasma gene sequences in human leukocytes was not defined.
- Diagnostic criteria were not defined to characterize a patient as "recovered", "fully recovered" or in a state of "relapse" during or following antibiotic therapy.
- A possible placebo effect has not been investigated.